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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
08/19/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/575,438	WHEELER ET AL.	
	Examiner	Art Unit	
	LAURA B. GODDARD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-7,11 and 25-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-7,11,25-28,30-34 and 40* is/are rejected.

7)☒ Claim(s) *29 and 35-39* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/4/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed June 4, 2010 in response to the Office Action of February 4, 2010, is acknowledged and has been entered. Claims 1-3, 5-7, 11, 25-40 are pending and being examined. Claims 27-40 are new. Claims 4, 8-10, and 12-24 are canceled.

Claim Objections

2. Claims 29 and 35-39 are free of the art but are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Maintained Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. **Claims 1-3, 5-7, 11, 25, and 26 remain rejected and new claims 27, 28, 30-34, and 40 are rejected under 35 U.S.C. 112, first paragraph**, because the specification, while being enabling for a method for treating a glioma in a mammal, the method comprising: (a) administering at least one vaccination of dendritic cells ("DC") to said mammal suffering from a glioma, **wherein said DC are primed *ex vivo* with autologous glioma cells**; and (b) after glioma recurrence following (a), administering a

regimen of chemotherapy to said mammal, wherein said regimen of chemotherapy includes the administration of at least one chemotherapeutic agent selected from the group consisting of temozolomide, procarbazine, vincristine, BCNU, CCNU, thalidomide, irinotecan, isotretinoin, imatinib, etoposide, and combinations thereof, does not reasonably provide enablement for said method comprising *administering DC that are not primed, or that are primed with any unknown source*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims (see section 2 of the previous Office Action).

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state

of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The specification discloses administering dendritic cells (DC) to newly diagnosed glioblastoma multiforme (GBM) patients, wherein patients received three vaccines, two weeks apart of 10-40X10^6 autologous DC loaded with either HLA7 eluted peptides from cultures tumor cells of 150 ug/ml autologous tumor freeze-thaw lysate, starting approximately fifteen weeks post-surgery. The specification points to Yu et al (Cancer Research, 2001, 61:842-847, IDS) in Example 4, p. 17, to describe how blood was collected and vaccinations were administered. Yu et al teach that GBM patients' peripheral blood stem cells were collected and expanded *ex vivo* into DCs and pulsed with peptides eluted from the surface of cultured autologous brain tumor cells (p. 842, col. 1). The specification discloses that GBM patients receiving chemotherapy after vaccination with DC exhibited significantly prolonged survival relative to those receiving either treatment individually (Example 2; p. 13).

One cannot extrapolate the disclosure of the specification to the scope of the claims because the specification does not provide guidance or examples for treating glioma in patients comprising administering **DCs that are not primed**. The specification discloses only treatment of glioma by administration of DCs primed *ex vivo* with autologous tumor cells. The art teaches that unprimed or unpulsed DCs are ineffective for treating tumors. Okada et al (Int J Cancer, 1998, 78:196-201) teach that non-peptide-pulsed DCs failed to protect mice from brain tumor challenge (Figure 1 and 2). Liau et al (J Neurosurgery, 1999, 90:1115-1124) teach that rats with intracranial 9L

gliomas treated with unpulsed DCs had a significantly shorter survival time than rats treated with tumor antigen-pulsed DCs, and the survival time for rats treated with unpulsed DCs was the same as that of rats treated with control media (p. 1118, col. 1-2; Figure 4). Heimberger et al (J of Neuroimmunology, 2000, 103:16-25) teach that vaccination with unpulsed DCs did not protect mice against glioma challenge and had the same effect as phosphate-buffered saline, where as DCs pulsed or primed with glioma tumor protected mice against intracerebral challenge glioma cells (p. 20, col. 1; Figure 2). Given the teaching of the art, one of skill in the art could not predictably treat glioma in a mammal comprising administering DCs that are not primed because they fail to initiate an immune response that can treat.

One cannot extrapolate the disclosure of the specification to the scope of the claims because the specification does not provide guidance or examples for treating glioma in patients comprising administering **DCs that are primed *ex vivo* with any unknown antigen or source**. The claims as currently constituted recite “wherein said DC are primed *ex vivo*." The art teaches that DCs must be primed with antigens expressed on the tumor being treated in order to be effective. Okada et al (above) teach that DCs pulsed with control peptides (control influenza peptides, “I-DC”), or peptides not expressed on the tumor, failed to protect mice from tumor challenge (Figure 1 and 2), whereas DCs pulsed with antigen expressed on the tumor (E7) were able to protect mice from tumor challenge. Zhang et al (Clinical Cancer Research, 2007, 13:566-575) teach that there are numerous and highly variable expression of tumor associated antigens on gliomas (p. 566, col. 2 to p. 567, col. 1; Table 2 and 3). Zhang et al teach

that effective immunotherapy requires that the patients' neoplasm displays the tumor antigen properly associated with their restricted HLA alleles. This allows T-cell clonal expansion after their recognition. Given the teaching of the art, one of skill in the art could not predictably treat glioma in a patient with DCs primed *ex vivo* with any unknown antigen or source, other than primed with the patient's autologous glioma cells that express the antigens required to be targeted by the DCs.

Therefore, in view of the state of the art, the quantity of experimentation necessary, the breadth of the claims, lack of guidance in the specification, and the absence of working examples for treating glioma with DCs that are not primed, or primed with any source, it would require undue experimentation for one skilled in the art to practice the invention as broadly claimed.

Response to Arguments

4. The rejection above is maintained with regards to claims broadly drawn to treating glioma in a mammal comprising administering DC that are not primed or that are primed with any unknown source. The rejection with regards to lack of enablement for administering allogeneic DC is withdrawn in view of Applicants' arguments.

5. With regards to claims broadly drawn to treating glioma in a mammal comprising administering DC that are not primed, Applicants argue that the instant application teaches that unprimed DCs may be used in the claimed methods and can be delivered to a tumor bed or tumor region without first being primed *ex vivo* and that the DC

process the tumor antigens *in vivo*. Applicants argue that the application incorporates reference US 2004/0057935 that provides a working example of prolongation of survival of animals with new and established tumors by administration of unprimed dendritic cells intracranially (Example 4 and 5). Applicants argue that Ehtesham et al discloses that unprimed DCs were effective to inhibit tumor growth and prolong survival of animals with gliomas when administered intratumorally. Applicants argue that Okada describes intravenous administration of DC and Liau describes subcutaneous DC administration. Applicants argue that one of ordinary skill would recognize based on the state of the art at the time of filing that the guidance and examples provided in the instant specification that either unprimed or primed DCs would be used in the claimed methods and could alter the means of administration based on the priming state of the DCs if necessary (p. 6-7).

The arguments have been considered but are not found persuasive. As stated in the rejection: The art teaches that unprimed or unpulsed DCs are ineffective for treating tumors. Okada et al (Int J Cancer, 1998, 78:196-201) teach that non-peptide-pulsed DCs failed to protect mice from brain tumor challenge. Liau et al teach that rats with intracranial 9L gliomas treated with unpulsed DCs had a significantly shorter survival time than rats treated with tumor antigen-pulsed DCs, and the survival time for rats treated with unpulsed DCs was the same as that of rats treated with control media. Heimberger et al teach that vaccination with unpulsed DCs did not protect mice against glioma challenge and had the same effect as phosphate-buffered saline, where as DCs pulsed or primed with glioma tumor protected mice against intracerebral challenge

glioma cells. Although one of ordinary skill would know logistically how to administer an unprimed DC by different routes, as Applicants argue, given the teaching of the art, one of skill in the art could not predictably treat glioma in a mammal comprising administering DCs that are not primed because they fail to initiate an immune response that can treat, therefore, undue experimentation would be required to practice the invention as broadly claimed.

With regards to Applicants' arguments that DCs may be delivered to a tumor bed or tumor region without first being primed *ex vivo* and that the DC process the tumor antigens *in vivo*, the arguments are not persuasive because Applicants are providing examples of and arguing enablement for limitations not recited in the claims, therefore Applicants' examples and arguments are not commensurate in scope with the broadly claimed invention. Applicants are essentially arguing that glioma treatment works when DCs are primed *in vivo*, which requires direct exposure of the DCs to tumor or tumor antigens, hence the DCs are primed. US 2004/0057935 Example 4 demonstrates direct inoculation of DCs mixed with irradiated and viable glioma cells followed by intratumoral DC inoculation, hence the DCs were exposed to glioma cells and primed, which is not a limitation recited in the instant claims. Example 5 of US 2004/0057935 demonstrates intracranial inoculation of rats with viable glioma cells followed by intracranial inoculation of DCs, hence the DCs were inoculated directly into the tumor area and primed by tumor cells, which is not a limitation recited in the instant claims. In Ehtesham et al, the DCs are either mixed with glioma cells and primed before inoculation into rats, or were inoculated directly into tumors for priming, which is not a limitation recited in the instant

claims. The claims are broadly drawn to administration of DCs to a mammal suffering from glioma, hence the claims are broadly drawn to administration of DCs anywhere in the mammal and DCs that are not primed. Such administration would not predictably treat glioma for the reasons of record.

6. With regards to claims broadly drawn to treating glioma in a mammal comprising administering DC that are primed with any unknown source, Applicants argue that even unprimed DCs can be used in the claimed methods. Applicants argue that if DCs are to be primed *ex vivo*, sources of antigen other than the patients autologous dendritic cells (Examiner believes Applicants intended to state autologous "tumor" here rather than "dendritic cells"), can also be used. Applicants argue that the specification contemplates that DCs can be primed by numerous methods, e.g. with tumor associated antigens as peptides, proteins, tumor cell lysates or elutes, DNA, RNA, or expressed by viral or non-viral vectors transfected into DCs. Applicants argue that Okada discloses the use of dendritic cells pulsed with synthetic peptide ($E7_{49-57}$) expressed on the tumor cells and this treatment was effective in 67% of animals treated, whereas treatment with a control influenza peptide not expressed on the tumor cells was not effective (p. 7-8).

Applicants argue that Liu et al discloses several tumor-associated antigens shared by gliomas that have been identified. Applicants argue that Liu observed an immune response against a TRP-2 peptide and this response was found to induce chemosensitivity of gliomas in methods similar to those claimed. Applicants argue that Parmiani et al describes phase I and II clinical trials using tumor associated antigen

peptides (gp100, tyrosinase, and MAGE-3) in which patients exhibited a response to the treatment, indicating that peptides can be a source of antigen for DC therapy. Zhang et al describes several antigens associated with gliomas. Casey et al describes a protein isolated from a non-autologous tumor used in a DC vaccine. Applicants argue that several sources of antigen were known at the time of filing for priming DCs. Applicants argue undue experimentation is not necessary to practice the invention using unprimed DCs or DCs primed *ex vivo*.

The arguments have been considered but are not found persuasive. Although one of ordinary skill in the art could logistically and routinely prime DCs with any antigen including tumor associated antigens as peptides, proteins, tumor cell lysates or elutes, DNA, RNA, or expressed by viral or non-viral vectors transfected into DCs, the art teaches that DCs must be primed with antigens expressed on the tumor being treated in order to predictably treat the tumor. As stated in the rejection: Okada et al (above) teach that DCs pulsed with control peptides (control influenza peptides, "I-DC"), or peptides not expressed on the tumor, failed to protect mice from tumor challenge (Figure 1 and 2), whereas DCs pulsed with antigen expressed on the tumor (E7) were able to protect mice from tumor challenge. Zhang et al teach that there are numerous and highly variable expression of tumor associated antigens on gliomas (p. 566, col. 2 to p. 567, col. 1; Table 2 and 3). Zhang et al teach that effective immunotherapy requires that the patients' neoplasm displays the tumor antigen properly associated with their restricted HLA alleles. This allows T-cell clonal expansion after their recognition. Given the teaching of the art, one of skill in the art could not predictably treat glioma in a patient

with DCs primed *ex vivo* with any unknown antigen or source, other than primed with the patient's autologous glioma cells that express the antigens required to be targeted by the DCs.

Applicants' arguments drawn to Okada reinforce Examiner's arguments that the tumor antigen used to prime the DCs must be expressed by the tumor being treated in order to predictably treat the tumor. Applicant's arguments drawn to references that identify antigens expressed in gliomas are not persuasive because no treatment of gliomas using unidentified antigens, unidentified sources, or antigens not expressed by glioma as broadly encompassed by the claims are demonstrated or enabled. Further, although Applicants argue glioma tumor antigens are known, none of the rejected claims recite any glioma tumor antigens used to prime the DCs, hence Applicants are arguing limitations not recited in the claims. Applicants' arguments reinforce Examiner's position that the DCs must be primed with glioma antigens that are expressed by the gliomas being treated in order to predictably treat glioma. Further, as stated above, Zhang et al teach that there are numerous and highly variable expression of tumor associated antigens on gliomas, therefore one of skill in the art cannot predictably treat glioma using DCs primed with any antigen because glioma antigen expression is highly variable, hence priming of DCs with autologous glioma enables priming of DCs with antigen expressed in the glioma being treated. The claims as currently constituted are broadly drawn to treating glioma in a mammal comprising administering DCs that are either unprimed or are primed with any unknown source. Applicants' arguments are not persuasive for enabling the treatment of glioma comprising administering DCs that are

primed with any unknown antigen including those not expressed by the glioma being treated in the mammal.

It is further noted that Examiner is not rejecting the form of antigen, that is if the antigen is a peptide, protein, tumor cell lysates or elute, etc., Examiner is rejecting claims broadly drawn to priming DCs with any unknown sources or anything irrelevant to antigens expressed on the glioma being treated.

7. **Conclusion:** No claim is allowed. Claims 29 and 35-39 are objected to. Claims 1-3, 5-7, 11, 25, 26-28, 30-34, and 40 are rejected.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. ' 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. ' 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA B. GODDARD whose telephone number is (571)272-8788. The examiner can normally be reached on 7:00am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Laura B Goddard/
Primary Examiner, Art Unit 1642